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10/672,069	09/25/2003	Tariq M. Rana	UMY-062RCE	4721

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,069	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,19,21,22,27,33-36,39-63,84-108* is/are pending in the application.

4a) Of the above claim(s) *19,21,22,27,34-36,40-63 and 91-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,33,39 and 84-90* is/are rejected.

7)☒ Claim(s) *1 and 86* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 08/12/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 02/12/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 08/12/2009, claims 1, 3, 4, 33, 39 and 84-90 are under examination and claims 19, 21-22, 27, 34-36, 40-63 and 91-108 are withdrawn from further consideration as being drawn to a non-elected invention.

New Claim Rejections – necessitated by claim amendments

Claim Objections

Claim 86 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 86 recites the antisense strand is modified by the substitution of at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense and fails to further limit claims 1, 84 and 85 which recites the antisense strand comprises at least one 2'-deoxy adenosine or 2'-

deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense.

Claim 1 objected to because of the following informalities: The word "cleavange" in the fourth line appears to be a misspelling of the word "cleavage". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 33, 39 and 84-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 3, 4, 33, 39 and 84-90 are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein the antisense strand comprises at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand, wherein the antisense strand is modified such that each uridine is a 2'-fluoro

uridine and each cytidine is a 2'-fluoro cytidine such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA and further drawn to each uridine is a 2'-fluoro uridine and each cytidine is a 2'-fluoro cytidine on the sense strand.

Applicant points to Figure 13 for support of the claim amendments. The siRNA structures shown in Figures 13A and 13B provide illustrative support for the instant claims wherein the target mRNA is EGFP and wherein the antisense strand comprises at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand. The instant specification fails to provide adequate support for siRNA targeted to any mRNA wherein the antisense strand comprises at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand. The breadth of the instant claims encompasses knowing the cleavage site of any target mRNA as well as the sequences of the target region and the siRNA. The specification does not specifically disclose the cleavage site of all known target mRNA and does not disclose siRNA sequences to all known target mRNA such that an adenosine or guanosine within 2 nucleotides upstream or 9 nucleotides downstream of the cleavage site is readily apparent.

Therefore, the instant specification does not provide adequate support for the breadth of the instant claims. If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity i.e. page and line, to where such support is to be found.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 33, 39 and 84-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (US 2004/0192626)

The claims are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein the antisense strand comprises at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand, wherein the antisense strand is modified such that each uridine is a 2'-fluoro uridine and each cytidine is a 2'-fluoro cytidine such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA and further drawn to each uridine is a 2'-fluoro uridine and each cytidine is a 2'-fluoro cytidine on the sense strand, wherein the siRNA retains the ability to inhibit expression of the target mRNA by at least 30% and wherein the siRNA further comprises a cleavage site for RISC and drawn to a composition comprising said siRNA and a pharmaceutically acceptable carrier.

For purposes of applying prior art, the limitation in the claims reciting "the antisense strand comprises at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand" is being interpreted such that at least one 2' deoxy

adenosine or guanosine can be located at nucleotides 6-10 and 17-21 from the 5' end of the antisense strand based on the location of the cleavage site on a target mRNA as described in the specification at page 14. The specification defines the cleavage site as 8-12 nucleotides from the 5' end of the antisense strand and because the claims are not drawn to a particular siRNA sequence nor any specific configuration of modified nucleotides in the siRNA, the location of the substitution of at least one 2' deoxy adenosine or guanosine nucleotide can be located at nucleotides 6-10 and 17-21 from the 5' end of the antisense strand based. The following prior art rejection is based on this interpretation.

McSwiggen et al. teach siRNA molecules comprising two strands of about 18 to 27 nucleotides in length wherein one or both strands can be chemically modified and comprises 2 nucleotide 3' overhang regions (see paragraphs 0013-0015). McSwiggen et al. teach the siRNA molecules target and silence cellular or viral gene expression and teach pharmaceutical compositions comprising said siRNA molecules (see at least paragraphs 0194 and 0154). McSwiggen et al. teach the antisense and/or the sense strand can comprise combinations of modified nucleotides such as 2' fluoro groups as well as 2'-deoxy groups and teach specific embodiments wherein the antisense strand comprises pyrimidine nucleotides modified with a 2'-fluoro and purine nucleotides modified with 2'-deoxy groups (see at least paragraphs 0026, 0027, 0057 and 0107). McSwiggen et al. exemplifies a siRNA wherein the pyrimidines are substituted with 2'-fluoro groups and the purines are substituted with 2'-deoxy groups on both the sense and antisense strands wherein a 2'-deoxy adenosine or guanine is located at

nucleotides 6-10 and 17-21 from the 5' end of the antisense strand which would meet the limitations of the instant claims as explained above (see Figures 18F and 19F). The modified siRNA taught by McSwiggen et al. has priority in WO 03/074654, Figures 18 and 19.

At paragraph [0011-0012], McSwiggen et al. teach the introduction of chemically modified nucleotides provide a powerful means to overcome the limitations of in vivo stability and bioavailability inherent to native RNA molecules and teach the modified siRNA molecules have increased stability but are able to still mediate RNAi (see paragraph 0111). McSwiggen et al. teach the siRNA molecule has a cleavage site for RISC which mediates cleavage of the target gene (see paragraph 0005) and references the work of Elbashir et al. (Genes and Dev 2001 also cited on IDS filed 02/27/2006) which identifies the cleavage region of siRNA.

McSwiggen et al. do not specifically teach the siRNA comprising modified nucleotides retains the ability to inhibit expression of the target mRNA by at least 30% however beginning at paragraph [0315] McSwiggen et al. teach optimizing the activity of the siRNA comprising modified nucleotides to preserve the ability of the siRNA to mediate RNAi efficiently in cells. It would have been obvious to one of ordinary skill in the art to synthesize a siRNA comprising chemically modified nucleotides as taught above and optimize the incorporation of said modifications to obtain a siRNA with the highest ability to inhibit the desired gene expression.

Beginning in Example 1, McSwiggen et al. teach detailed steps on constructing the said siRNA molecules and methods of testing the activity of said siRNA against the

target gene. Given that McSwiggen et al. teach the introduction of chemically modified nucleotides provides a powerful means to overcome the limitations of in vivo stability and bioavailability inherent to native RNA molecules, one would have clearly incorporated said modifications into a siRNA and would have optimized the position and number of modified nucleotides to obtain a siRNA with the highest ability to inhibit the desired gene expression. Moreover, given that there are a multitude of general methods and strategies to determine the location of incorporation of chemically modified nucleotides as taught by McSwiggen et al., one of ordinary skill in the art would have expected to be able to determine the location of incorporation of chemically modified nucleotides as instantly claimed while maintaining the siRNAs ability to inhibit gene expression by at least 30%.

Thus, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the invention was made.

Response to Applicant's Arguments

Claim Rejections - 35 USC § 112

The rejected claims 1, 3-4, 33, 39 and 84-90 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record. The claims as amended would have been rejected under the previous rejection and therefore the response to Applicant's arguments will be addressed as to the amended claims.

Applicant argues that based on the instant application, one of ordinary skill in the art would be able to choose a target gene, determine the appropriate siRNA compositions and conduct routine assays in order to identify the siRNA meeting the functional limitations of the claims.

This argument is not persuasive because the claims are not drawn to a method of making a siRNA with the ability to inhibit expression of a target gene by 30% and the rejection is not based on a lack of enablement. As stated previously, to satisfy the written description requirement, MPEP §2163 states, in part "…a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "…disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The instant claims are drawn to siRNA comprising a sense strand and an antisense strand wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA, wherein the antisense strand and/or sense strand comprise modifications as claimed such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA and wherein the siRNA retains the ability to inhibit expression of the target mRNA by at least

30%. The instant claims and specification fail to provide adequate written description of the entire genus of siRNA wherein the antisense strand and/or sense strand are modified such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA *and* wherein the siRNA retains the ability to inhibit expression of a target mRNA by at least 30%.

The specification does describe in Figure 13B siRNA sequences targeted to an EGFP mRNA wherein the siRNA comprises the modification as claimed. However, it does not appear the modified siRNA retained the ability to inhibit expression of the EGFP target mRNA by at least 30% as compared to the unmodified siRNA in the in vitro experiment (lanes 25-42). The specification does not have adequate written description for the entire genus comprising siRNA targeted to any target gene comprising any number of modified nucleotides that are capable of inhibiting the expression of said target gene by at least 30%. The skilled artisan would not know from the disclosure of siRNA targeted to EGFP that this siRNA is capable of inhibiting expression from any other target gene by at least 30%.

As stated previously, the specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention and the state of the art cannot provide the specific guidance as evidenced by Holen et al. (Nucleic Acids Research 2002, Vol. 30, No. 8: 1757-1766 cited of IDS filed 11/20/07). Holen et al. teach that several siRNAs targeted against the same target gene demonstrated striking differences in silencing efficiency (see page 1757). The instantly claimed siRNA are not recognizable by their design that they are synthesized as capable of inhibiting the

expression of any target gene by at least 30%. The instant specification nor the prior art provide the specific guidance to construct siRNA comprising modified nucleotides that are capable of silencing any gene expression by at least 30%. Because the prior art teach even siRNA synthesized to the same target gene demonstrate strikingly different degrees of gene silencing, one of skill in the art would not know which sequence of a broad genus of modified siRNA claimed targeted against any target would provide the necessary activity of silencing gene expression by at least 30% as compared to unmodified siRNA.

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of modified siRNA capable of silencing gene expression of any target gene by at least 30%.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 103

The rejection of claims 1, 3, 4, 33, 39 and 84-90 under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (US 2003/0143732) is withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Tracy Vivlemore at 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kimberly Chong/
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